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Original Research Article

Reduced SARS-CoV-2 infection risk is associated with the use of Seven-Flavor Herb Tea: a multi-center observational study in Shanghai, China

Shun-Xian Zhang[a,1], Xiao-Xu Chen[b,1], Yong Zheng[c], Bing-Hua Cai[d], Wei Shi[e], Ming Ru[f], Hui Li[g], Dan-Dan Zhang[h], Yu Tian[b*], Yue-Lai Chen[i*]

[a] Clinical Research Center, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200032, China
[b] Medical Affairs Department, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200032, China
[c] Medical Affairs Department of Minhang District Health Committee, Shanghai 201199, China
[d] Medical Affairs Department of Fengxian District Health Committee, Shanghai 201499, China
[e] Medical Affairs Department of Jinshan District Health Committee, Shanghai 200540, China
[f] Medical Affairs Department of Xuhui District Health Committee, Shanghai 200030, China
[g] Medical Affairs Department of Changning District Health Committee, Shanghai 200050, China
[h] Medical Affairs Department, Jinshan TCM-Integrated Hospital, Shanghai 201501, China
[i] Sleep Medicine Center, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200032, China

ABSTRACT

Objective: Omicron, a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant, is responsible for numerous infections in China. This study investigates the association between the use of Seven-Flavor Herb Tea (SFHT) and the risk of SARS-CoV-2 infection to develop precise and differentiated strategies for control of the coronavirus disease 2019 (COVID-19).

Methods: This case-control study was conducted at shelter hospitals and quarantine hotels in China. A total of 5348 laboratory-confirmed COVID-19 patients were enrolled between April 1 and May 31, 2022, while 2190 uninfected individuals served as healthy controls. Structured questionnaires were used to collect data on demographics, underlying diseases, vaccination status, and use of SFHT. Patients were propensity-score-matched using 1:1 nearest-neighbor matching of the logit of the propensity score. Subsequently, a conditional logistic regression model was used for data analysis.

Results: Overall, 7538 eligible subjects were recruited, with an average age of [45.54 ± 16.94] years. The age of COVID-19 patients was significantly higher than that of uninfected individuals ([48.25 ± 17.48] years *vs* [38.92 ± 13.41] years; $t = 22.437$, $P < 0.001$). A total of 2190 COVID-19 cases were matched with uninfected individuals at a 1:1 ratio. The use of SFHT (odds ratio = 0.753, 95% confidence interval: 0.692, 0.820) was associated with a lower risk of SARS-CoV-2 infection compared to untreated individuals.

Conclusion: Our findings suggest that taking SFHT reduces the risk of SARS-CoV-2 infection. This is a useful study in the larger picture of COVID-19 management, but data from large-sample multi-center, randomized clinical trial are warranted to confirm the finding.

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Correspondence: Yu Tian; E-mail addresses: tyrain2000@sina.com. Yue-lai Chen; E-mail addresses: chenyuelai@163.com.
[1] Shun-Xian Zhang and Xiao-Xu Chen contributed equally to this work.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses a significant threat to public health [1,2]. The first COVID-19 case was diagnosed in 2019, and the initial vaccines became available 18 months later [3]. New variants continue to emerge globally, with many classified as variants of concern due to their high transmissibility and reduced response to vaccination [4,5]; multiple highly infectious variants have been identified, including alpha (B.1.1.7), beta (B.1.351), gamma (P1), delta (B.1.617.2), lambda (C.37) and omicron (B.1.1.529) [5,6]. The omicron variant was first detected in Africa in early November 2021 and rapidly became the predominant pathogenic strain worldwide [6,7]. The emergence of the omicron lineage BA.2, characterized by strong infectivity, rapid transmission, low pathogenicity and high concealment, has led to a surge in COVID-19 cases in various countries and regions, presenting significant challenges to global control of the epidemic and posing a severe threat to human health.

The fight against the COVID-19 pandemic has been impeded by interconnected factors, including vaccine hesitancy, inconsistent global coordination, and inequitable distribution of supplies, vaccines and treatment drugs [3,5,7]. Despite the development and deployment of multiple vaccines in the past three years [8–10], the relaxation of non-pharmaceutical interventions (NPIs) and waning vaccine efficacy have contributed to the widespread resurgence of infections [11–15]. In addition, the existing antivirals (remdesivir, favipiravir, ribavirin, lopinavir, ritonavir, darunavir, arbidol, chloroquine and hydroxychloroquine) have proven ineffective against SARS-CoV-2 infection [11,12,16]. In March 2022, a large-scale outbreak of COVID-19 in China was caused by the Omicron lineage BA.2 variant. This outbreak infecting over 600,000 people, impacted numerous close contacts, and had significant negative effects on social and economic development [17]. The rapid spread of the highly contagious Omicron variant has prompted the frequent implementation of strict lockdown measures, sparking public discontent. Consequently, there is an urgent need for novel intervention measures to slow down the community transmission.

Traditional Chinese medicine (TCM) provides a significant part of global pharmaceutical science [18–22], with millennia of valuable experience in the use of Chinese herbs, and has considerable potential for COVID-19 treatment [19,23]. TCM theories on infectious diseases emerged during the Tang, Song and Yuan dynasties, culminating in the 17th century with the world's first systematic study of acute epidemic disease in the *Treatise on Exogenous Febrile Disease*, which detailed the etiology, pathogenesis, syndromes and treatments of the plague [24,25]. Previous studies have demonstrated that TCM can reduce mortality in critically ill, hospitalized COVID-19 patients and lower SARS-CoV-2 prevalence [20,26–28]. Consequently, there is a growing global interest in the use of TCM to combat SARS-CoV-2 and to develop interventions that prevent COVID-19 progression [29–32]. The National Health Commission of China has recommended several TCMs for addressing the COVID-19 pandemic, reflecting renewed confidence in their unique characteristics and benefits. TCM granules have been extensively promoted and recommended for all susceptible individuals in Shanghai, China, throughout the pandemic. Therefore, the case-control study was conducted among COVID-19 patients and uninfected individuals to evaluate the association between Seven-Flavor Herb Tea (SFHT) use and SARS-CoV-2 infection, providing a reference for implementing comprehensive strategies and measures to control COVID-19.

2. Methods

2.1. *Study design and setting*

This multi-center, case-control study aimed to ascertain the role of SFHT consumption in preventing COVID-19 during the outbreak caused by the SARS-CoV-2 Omicron variant in Shanghai. The study was conducted in six shelter hospitals and four medical quarantine hotels located in Shanghai from April to May 2022. Cases were recruited from the Shanghai National Exhibition and Convention Center [33], Jinshan Shelter Hospital, Tangzhen Shelter Hospital, Huangpu Shelter Hospital, Chongming Shelter Hospital and Zhoupu Shelter Hospital. Additionally, non-infected individuals were selected from Shanghai Hongqiao Jinjiang Hotel, Season Hotel in Meilong Town, Jinshan Sea Cube Hotel, and Hujia Hotel in Wuzhen Town between April 1 and May 31, 2022.

2.2. Participants

At the onset of the COVID-19 outbreak in late March 2022, the Shanghai municipal government provided TCMs to all residents as a preventive measure against the SARS-CoV-2 Omicron variant. The initiative included five TCM prescriptions; however, the present study focused on one prescription known as SFHT (medicated tea). This prescription was provided to over a million individuals from April 1 to May 31, 2022. SFHT refers to a drink made by boiling several herbs with water. It possesses certain activities and has become a popular daily healthcare approach in China. The SFHT granules were formulated as a mixture (extracts of Astragalus Membranaceus 9.0 g, Radix Ginseng 3.0 g, Rhizoma Phragmitis 9.0 g, Lonicerae Japonicae Flos 5.0 g, Mentha Haplocalyx Briq 3.0 g, Folium Perillae 3.0 g and Pogostemonis Herba 3.0 g) for single administration and packed in food-grade plastic bags (26.0 g/bag). Individuals voluntarily took SFHT prescriptions orally twice a day for more than one day before entering the shelter hospital or medical isolation hotel.

Upon the arrival of confirmed COVID-19 patients at the selected shelter hospitals, posters were used to recruit cases. Inclusion criteria were: (1) currently residing in Shanghai, (2) testing positive for SARS-CoV-2 by quantitative fluorescence polymerase chain reaction (PCR), and (3) consumption or non-consumption of SFHT. Exclusion criteria were: (1) mental disorders, (2) individuals unable to provide comprehensive information due to limited educational background or other factors, (3) refusal to participate in the study, and (4) consumption of other TCMs for prevention or treatment of viral respiratory diseases within one week of enrollment.

For uninfected individuals (control group), posters were used to recruit participants as they entered the medical isolation observation hotels. Specific inclusion criteria were: (1) currently residing in Shanghai, (2) having high-risk status determined by the Center for Disease Control and Prevention, such as close contact with cohabitants or colleagues confirmed to have COVID-19, (3) testing negative for SARS-CoV-2 by quantitative fluorescence PCR upon entering the isolation sites, and (4) remaining SARS-CoV-2 nucleic acid-negative during a week-long medical observation period and upon departure. Exclusion criteria were: (1) mental disorders, (2) individuals unable to provide comprehensive information due to limited educational background or other factors, (3) refusal to participate in the study, and 4) consumption of other TCMs for prevention or treatment of viral respiratory diseases within one week of enrollment.

A negative SARS-CoV-2 result was defined as having at least two consecutive negative real-time PCR tests taken at least 24 hours apart. SARS-CoV-2 nucleic acid was considered negative if the cycle threshold (Ct) values of the ORF1ab gene and the N gene were both above 35 [27].

2.3. Sampling and sample size

A preliminary investigation revealed a COVID-19 prevalence of 0.29% (10/3438) in individuals consuming SFHT (twice a day, for more than 3 days) and 1.73% (39/2248) in those not consuming SFHT. The sample size was calculated using the "Proportions > Two Independent Proportions" module in PASS 21 software (NCSS, LLC. Kaysville, Utah, USA). With a 1:1 group ratio, a two-sided α of 0.05, and a power of 0.80, a total of 1,210 subjects were required per group. Anticipating a 20% loss to follow-up, at least 1,513 subjects were recruited per group, resulting in a minimum sample size of 3,026 subjects.

2.4. Ethical approval

The study received approval from the Ethical Review Committee of Longhua Hospital (No: 2022LCSY027). All experimental procedures adhered to the *Declaration of Helsinki*, and written informed consent was obtained from all participants after explaining the study's purpose, potential risks and benefits.

2.5. Data collection

An electronic questionnaire was designed with the assistance of a computer expert and administered using the online survey tool Wenjuanxing (WJX, https://www.wjx.cn/ in Chinese). The collected data included (Supplementary file): (1) basic information such as age, gender, smoking history and drinking history; (2) underlying diseases, such as circulatory system, respiratory system and digestive system diseases, diabetes mellitus, tumour, chronic kidney disease, chronic liver disease, rheumatic immune disease and thyroid disease; (3) COVID-19 vaccination status before entering the shelter hospital or medical isolation hotels; and (4) history of SFHT use and other TCM drugs used before entering the shelter hospital or medical isolation hotel. The study team evaluated and controlled the questionnaire's efficiency and sensitivity, while trained medical staff in the shelter hospital and close contact hotels conducted the study.

2.6. Statistical analysis

The Kolmogorov-Smirnov test confirmed the normal distribution of quantitative data. Normally distributed data (age) were reported as mean ± standard deviation, with Student's *t*-test used for comparing means between two groups. Categorical variables were presented as frequencies and proportions and evaluated using Chi-squared or Fisher's exact tests. To maximize statistical power and minimize missing data bias, multivariate multiple imputation strategies based on five replications and the Markov chain Monte Carlo method were applied to fill missing covariates. Risk factors for SARS-CoV-2 infection were identified using univariate analysis. Factors with a P value < 0.20 in univariate analysis were included in the multivariate logistic regression model. A series of incremental models with different confounding factors were applied: Model 1 included SFHT use only; Model 2 adjusted for gender and age; Model 3 adjusted for taking SFHT, gender, age, smoking, drinking alcohol and home quarantine; Model 4 adjusted for taking SFHT, gender, age, smoking, drinking alcohol, home quarantine, underlying disease and vaccination. Additionally, propensity score matching (PSM) was conducted to adjust confounding factors. Propensity scores underwent 1:1 nearest-neighbor matching of the logit of the propensity score with a caliper width of 0.01 and 0.02, performed without replacement, and the data were analyzed using conditional logistic regression model.

Sensitivity analyses were conducted to assess the robustness of our findings using inverse probability of treatment weighting (IPTW) and covariate balancing propensity score (CBPS) models. Both IPTW and CBPS models were adjusted by the same covariates included in the logistic model. The robustness of the results with regard to potential unmeasured or uncontrolled confounding and selection bias was assessed using instrumental variable analyses. Gamma (γ) and delta (Δ) variables were used to determine the strength of any unmeasured confounding factors needed to overturn statistically significant results. The gamma and delta variables were assigned values of 0.00, 0.25, 0.50, 0.75 or 1.00. All statistical analyses were performed using R software version 4.2.1 (The R Foundation for Statistical Computing, https://cran.r-project.org/), and P < 0.05 was considered to indicate statistical significance.

3. Results

3.1. Participants' characteristics

From April 1 to May 31, 2022, a total of 7,538 eligible subjects were enrolled in this study (Fig. 1). In total, 40.5% of COVID-19 patients and 57.2% of non-infected individuals had used SFHT in the study. The baseline characteristics of the study participants prior to matching are presented in Table 1. The mean age of the participants was (45.54 ± 16.94) years, with the control group exhibiting a lower average age compared to the COVID-19 group ([38.92 ± 13.41] years *vs* [48.25 ± 17.48] years; $t = -22.347$, $P < 0.001$). Of the study participants, 18.33% (1382/7538) had underlying diseases, with the most prevalent being cardiovascular diseases (6.46%, 487/7,538), followed by respiratory disorders (5.40%, 407/7,538), gastrointestinal diseases (3.31%, 250/7,538), diabetes (2.92%, 220/7538) and neoplasms (0.69%, 52/7538). Notably, the prevalence of cardiovascular diseases, respiratory disorders, gastrointestinal diseases and diabetes was higher in the COVID-19 population compared to uninfected individuals (all $P < 0.05$, Table 1).

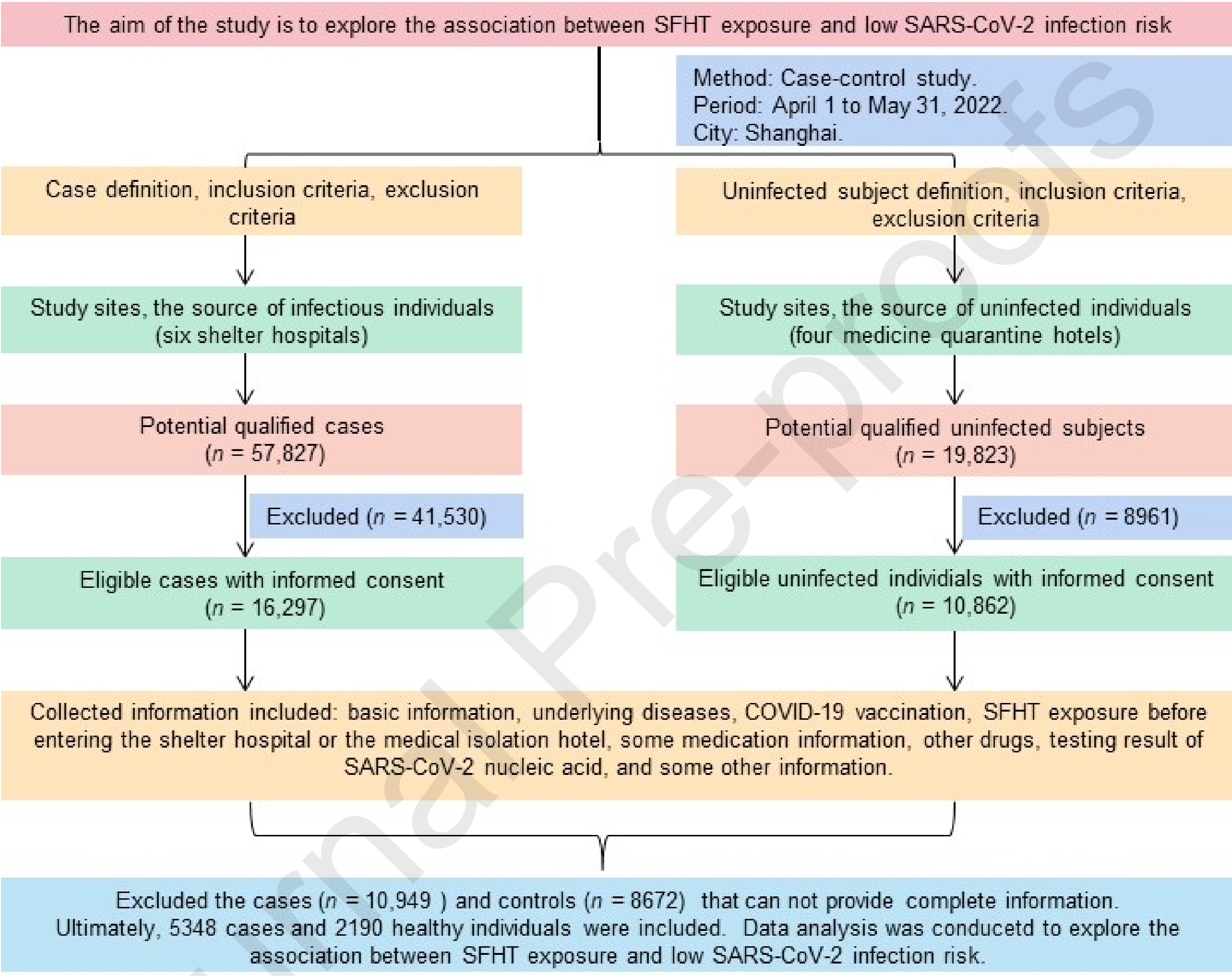

Fig. 1. Study flow chart. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SFHT: Seven-Flavor Herb Tea.

The case-control study was comprised 3051 females and 4487 males, with the average age of females significantly higher than that of males ([47.10 ± 17.97] years *vs* [44.48 ± 16.12] years; $t = 6.601$, $P < 0.0001$). In total, 6,358 participants were vaccinated, and 1,180 were unvaccinated; the average age of unvaccinated participants was significantly higher than that of vaccinated participants ([60.16 ± 19.42] years *vs* [42.46 ± 14.47] years; $t = 40.482$, $P < 0.0001$). Among the participants, 1,382 had underlying diseases, the average age of participants with underlying diseases was significantly higher than that of those without ([62.60 ± 15.49] years *vs* [41.71 ± 14.75] years; $t = 47.129$, $P < 0.0001$).
Furthermore, 4120 participants had taken SFHT. The average age of those who had not taken SFHT was significantly higher than that of those who had taken the medicine ([46.48 ± 17.88] years *vs* [44.41 ± 15.67] years; $t = 5.276$, $P < 0.0001$). The study included 5348 individuals with COVID-19 and 2190 healthy subjects, with the average age of the COVID-19 cases significantly higher than that of the uninfected individuals ([48.25 ± 17.48] years *vs* [38.92 ± 13.41] years; $t = 22.437$, $P <$

0.0001).

3.2. Factors related to SARS CoV-2 infection
Univariate analysis revealed that factors associated with COVID-19 included age, gender, home isolation, vaccination, underlying disease and use of SFHT (all $P < 0.001$; Table 1). Moreover, advanced age and the presence of underlying diseases were identified as risk factors for SARS-CoV-2 infection, whereas home isolation, vaccination and use of SFHT were linked to a reduced incidence of SARS-CoV-2 infection.

Table 1. Univariate analysis of factors relating to SARS-CoV-2 infection.

Variable	Subgroup	Uninfected individuals (N = 2190) (n [%])	COVID-19 patients (N = 5348) (n [%])	χ^2	P	OR (95% CI)
Age	< 60 years (n = 6013)	2045 (93.4)	3968 (74.2)	354.295	< 0.001	1 (Reference)
	≥ 60 years (n = 1525)	145 (5.6)	1380 (25.8)			4.905 (4.101, 5.868)
Gender	Female (n = 3051)	759 (34.7)	2292 (42.9)	43.359	< 0.001	1 (Reference)
	Male (n = 4487)	1431 (65.3)	3056 (57.1)			0.707 (0.638, 0.784)
Smoking	No (n = 5677)	1660 (75.8)	4017 (75.1)	0.532	0.466	1 (Reference)
	Yes (n = 1861)	530 (24.2)	1331 (24.9)			1.044 (0.931, 1.172)
Drinking alcohol	No (n = 1722)	1799 (82.1)	4017 (75.1)	0.394	0.531	1 (Reference)
	Yes (n = 5816)	391 (17.9)	1331 (24.9)			1.038 (0.924, 1.165)
Home quarantine	No (n = 2456)	492 (22.5)	1964 (36.7)	143.801	< 0.001	1 (Reference)
	Yes (n = 5082)	1,699 (77.5)	3384 (63.3)			0.499 (0.445, 0.560)
Vaccination	None (n = 1180)	111 (5.1)	1069 (20.0)	340.022	< 0.001	1 (Reference)
	1 dose (n = 295)	64 (2.9)	231 (4.3)			0.375 (0.267, 0.526)
	2 doses (n = 2395)	741 (33.8)	1654 (30.9)			0.232 (0.187, 0.287)
	3 doses (n = 3668)	1274 (58.2)	2394 (44.8)			0.195 (0.159, 0.240)
Underlying disease	No (n = 6156)	2024 (92.4)	4132 (77.3)	238.421	< 0.001	1 (Reference)
	Yes (n = 1382)	166 (7.6)	1216 (22.7)			3.588 (3.025, 4.256)
Circulatory system	No (n = 7045)	2,130 (97.3)	4915 (91.9)	72.529	< 0.001	1 (Reference)
	Yes (n = 487)	59 (2.7)	428 (8.0)			3.143 (2.383, 4.147)
Respiratory system	No (n = 7123)	2,139 (97.7)	4984 (93.2)	52.395	< 0.001	1 (Reference)
	Yes (n = 407)	54 (2.5)	353 (6.6)			2.806 (2.098, 3.753)
Digestive system	No (n = 7288)	2159 (98.6)	5129 (95.9)	34.784	< 0.001	1 (Reference)
	Yes (n = 250)	31 (1.4)	219 (4.1)			2.974 (2.035, 4.346)
Diabetes mellitus	No (n = 7318)	2163 (98.8)	5155 (96.4)	30.952	< 0.001	1 (Reference)
	Yes (n = 220)	27 (1.2)	193 (3.6)			2.999 (1.999, 4.501)
Tumour	No (n = 7471)	2182 (99.6)	5289 (98.9)	3.541	0.06	1 (Reference)
	Yes (n = 52)	9 (0.4)	43 (0.8)			1.971 (0.959, 4.051)
Other underlying disease	No (n = 7507)	2186 (99.8)	5321 (99.5)	0.605	0.437	1 (Reference)
	Yes (n = 23)	5 (0.2)	18 (0.3)			1.479 (0.548, 3.988)
Taking SFHT	No (n = 4120)	938 (42.8)	3182 (59.5)	174.173	< 0.001	1 (Reference)
	Yes (n = 3418)	1252 (57.2)	2166 (40.5)			0.510 (0.461, 0.564)

Statistical methods: Chi-square test. For basic diseases, one individual may have two or three basic diseases, so the total number of basic diseases among individuals exceeds the total number of individuals. CI: confidence interval; COVID-19: coronavirus disease 2019; OR: odds ratio; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SFHT: Seven-Flavor Herb Tea.

In the multivariate analysis, variables with $P < 0.20$ (age, gender, home quarantine, vaccination, underlying disease and use of SFHT) from the univariate analysis were included. Factors significantly associated with SARS-CoV-2 infection included age, gender, home quarantine, vaccination, underlying disease and use of SFHT (Table 2).

Table 2. Multivariate logistic regression analysis was conducted to explore affecting factor for COVID-19.

Variable	Coefficient	S.E.	Wald	*P* value	OR (95% CI)
Age	0.991	0.101	96.745	< 0.001	2.694 (2.211, 3.282)
Gender	–0.232	0.056	17.494	< 0.001	0.793 (0.711, 0.884)
Home quarantine	–0.608	0.061	99.784	< 0.001	0.544 (0.483, 0.613)
Underlying disease	0.712	0.095	56.089	< 0.001	2.038 (1.692, 2.455)
Vaccination	–0.817	0.111	54.305	< 0.001	0.442 (0.355, 0.549)
Taking SFHT	–0.564	0.054	110.816	< 0.001	0.569 (0.512, 0.632)
Constant	2.754	0.313	77.471	< 0.001	15.711

CI: confidence interval; COVID-19: coronavirus disease 2019; OR: odds ratio; S.E.: standard error; SFHT: Seven-Flavor Herb Tea.

3.3. Exploration of the relationship between the use of SFHT and reduced risk of SARS CoV-2 infection using multiple models to control for confounding factors

Multivariable logistic regression analysis was employed to construct several models. Model 1 included only individuals who had consumed SFHT as an independent variable, while Models 2, 3, and 4 were adjusted for different covariates. The risk of SARS-CoV-2 infection in individuals who had used SFHT was significantly lower than that in those who had not, with odds ratio (OR) values ranging from 0.510 to 0.546 ($P < 0.001$), respectively. These findings suggest an important association between use of SFHT and reduced risk of SARS-CoV-2 infection (Table 3).

Table 3 A series of incremental models with different confounding factors were adjusted to explore the association between SFHT exposure and low risk of SARS-CoV-2 infection.

Model	Variable	Coefficient	S.E.	Wald χ^2	*P*	OR (95% CI)
Model 1	Taking SFHT	–0.674	0.051	172.154	< 0.001	0.510 (0.461, 0.564)
Model 2	Taking SFHT, gender and age	–0.661	0.053	153.843	< 0.001	0.517 (0.466, 0.574)
Model 3	Taking SFHT, gender, age, smoking, drinking alcohol and home quarantine	–0.646	0.054	145.242	< 0.001	0.524 (0.472, 0.582)
Model 4	Taking SFHT, gender, age, smoking, drinking alcohol, home quarantine, underlying disease and vaccination	–0.606	0.054	125.703	< 0.001	0.546 (0.491, 0.607)

SFHT exposure includes taking SFHT and non-taking SFHT, and the non-taking SFHT is reference. Model 1: adjusted for none. Model 2: adjusted for gender and age. Model 3: adjusted for gender, age, smoking, drinking alcohol and home quarantine. Model 4: gender, age, smoking, drinking alcohol, home quarantine, underlying diseases and vaccination. CI: confidence interval; OR: odds ratio; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; S.E.: standard error; SFHT: Seven-Flavor Herb Tea.

3.4. Matching cases and controls using the PSM

Table 4 shows no significant differences in the association of SARS-CoV-2 infection with age, gender, smoking, alcohol consumption, home quarantine, vaccination or underlying disease, with all having *P* values less than 0.05 and standardized mean differences < 0.10, indicating a balanced equilibrium between COVID-19 patients and uninfected individuals after matching.

Table 4. PSM was conducted to match COVID-19 patients and uninfected individuals.

Variable	Subgroup	PSM (1:1), caliper width = 0.01				PSM (1:1), caliper width = 0.02			
		Uninfected individuals (N = 2190) (n [%])	COVID-19 patients (N = 2190) (n [%])	χ^2	P	Uninfected individuals (N = 2190) (n [%])	COVID-19 patients (N = 2190) (n [%])	χ^2	P
Age	< 60 years	2045 (93.4)	2045 (93.4)	0.001	0.999	2045 (93.4)	2058 (94.0)	0.651	0.421
	≥ 60 years	145 (6.6)	145 (6.6)			145 (6.6)	132 (6.0)		
Gender	Female	759 (34.7)	756 (34.6)	0.009	0.924	759 (34.7)	725 (33.1)	1.178	0.278
	Male	1431 (65.3)	1434 (65.5)			1431 (65.3)	1465 (66.9)		
Smoking	No	1660 (75.8)	1650 (75.3)	0.124	0.721	1660 (75.8)	1655 (75.6)	0.031	0.861
	Yes	530 (24.2)	540 (24.6)			530 (24.2)	535 (24.2)		
Drinking alcohol	No	1799 (82.1)	1789 (81.7)	0.154	0.695	1799 (82.1)	1784 (81.5)	0.345	0.557
	Yes	391 (17.9)	401 (18.3)			391 (17.9)	406 (15.5)		
Home quarantine	No	492 (22.5)	492 (22.5)	0.001	0.999	492 (22.5)	505 (23.1)	0.219	0.639
	Yes	1698 (77.5)	1698 (77.5)			1698 (77.5)	1685 (76.9)		
Vaccination	No	916 (41.8)	919 (42.0)	0.008	0.927	916 (41.8)	955 (43.6)	1.419	0.234
	Yes	1274 (58.2)	1271 (58.0)			1274 (58.2)	1235 (56.4)		
Underlying disease	No	2024 (92.4)	2024 (92.4)	0.001	0.999	2024 (92.4)	2017 (92.1)	0.157	0.682
	Yes	166 (7.6)	166 (7.6)			166 (7.6)	173 (7.9)		

Statistical methods: Chi-square test; COVID-19: coronavirus disease 2019; PSM: propensity score matching.

Univariate conditional logistic regression analysis revealed an association between the use of SFHT and reduced risk of SARS-CoV-2 infection with a caliper width of 0.01 (OR = 0.753, 95% CI: 0.692, 0.820). Conditional logistic regression analysis also demonstrated that the use of SFHT was associated with low SASR-CoV-2 infection risk compared to individuals not taking SFHT, with a caliper width of 0.02 (OR = 0.581, 95% CI: 0.513, 0.657).

3.5 Sensitivity analysis

Sensitivity analysis employing IPTW revealed statistically significant differences in the distribution of baseline and clinical characteristics between COVID-19 patients and healthy subjects who had used or not used SFHT. Based solely on Model 4, IPTW yielded effect estimates similar to those determined by adjustment of covariates in multivariate analysis, demonstrating the relationship between reduced infection risk and use of SFHT (OR = 0.632; 95% CI: 0.570, 0.700; $P < 0.001$). Unmeasured confounding factors also influenced the association between SFHT use and low SARS-CoV-2 infection risk. Adjusted ORs in Model 4, which included two new variables (gamma and delta), ranged from 0.633 (95% CI: 0.572, 0.701; $P < 0.001$) to 0.569 (95% CI: 0.512, 0.632). Consequently, these results demonstrate the stability of the association between SFHT use and reduced risk of SARS-CoV-2 infection.

4. Discussion

The association between the use of SFHT and SARS-CoV-2 infection was explored in this study. The integrated findings suggest that SFHT use is associated with a lower risk of SARS-CoV-2 infection, revealing novel opportunities for COVID-19 interventions. In response to the surge in both imported and domestic infections between February and June 2022, the Shanghai government adhered to its dynamic zero-COVID policy, promptly and decisively implementing a comprehensive set of measures to control the spread of the SARS-CoV-2 Omicron variant. These measures encompassed epidemiological investigation, mass nucleic acid testing, restricting population mobility, health education initiatives, and prophylactic therapy with antiviral drugs or TCM for all susceptible individuals [34,35]. The cultural and theoretical perspectives of TCM, guided by the "prevention and treatment of disease before its onset (治未病)" principle, foster health awareness [21,36], encouraging individuals to adopt proactive self-protection strategies. During the epidemic, such NPIs included wearing masks in public spaces, complying with regular nucleic acid testing requirements, disinfecting delivered packages, and washing hands upon returning home. Additionally, individuals prioritized regular exercise to promote overall health and robust immunity. A variety of interventions, such as regular exercise, sufficient sleep, maintaining a healthy weight, and spending time outdoors, have been shown to yield positive health outcomes in the context of the COVID-19 pandemic [32]. These measures and other healthy behaviors can reduce the risk of SARS-CoV-2 infection to some extent, and self-medication with TCM for symptom management or prevention during the COVID-19 pandemic serves as an indicator of heightened health awareness.

TCM has been reported to reduce the risk of SARS-CoV-2 infection, and network pharmacological studies showed that TCM contributes to immunoregulation in the management of COVID-19 through multiple components acting on various targets and pathways [37]. Nevertheless, mechanistic studies employing proteomics, immunology and metabonomics approaches have not provided biological evidence that drugs, including TCM, can prevent SARS-CoV-2 infection. Since the outbreak of COVID-19 in January 2020, TCM has played a pivotal role in combating the epidemic, working synergistically with modern drugs to achieve favorable prevention and treatment outcomes [38,39]. Traditional herbs offer the advantage of regulating and enhancing human immune function, stimulating the body's innate defense and resistance against SARS-CoV-2. Numerous components of ginseng, particularly ginsenosides and polysaccharides, exert various effects on immune enhancement [39,40], benefiting not only uninfected individuals but also those with compromised immune function. Similarly, Astragalus Membranaceus exhibits a preventive effect, with astragalus polysaccharides as one of its main components. Acting as an immune regulator, it can promote and regulate mucus secretion in the respiratory system, significantly impacting the primary immune defense in the human body. Astragalus flavonoids can also facilitate the activation of lymphocytes, macrophages and neutrophils, as well as improve macrophage phagocytosis, enabling a rapid response to invading pathogens and generating non-specific antiviral effects [39,40]. These herbal constituents may enhance immunity and combat viruses, which possibly explains the correlation between the consumption of traditional herbs and reduced risk of SARS-CoV-2 infection. Further in-depth research is necessary to ascertain whether plant-derived components can prevent viral infection.

5. Limitations

Certain limitations of this study must be acknowledged. The non-randomized study design precludes confirmation of the relationship between the timing of SFHT use and SARS-CoV-2 infection, due to recall and selection biases. Moreover, additional research efforts (prospective cohort studies and randomized controlled trials with large sample sizes) are necessary to establish a causal link between the use of SFHT and reduced risk of SARS-CoV-2 infection, ultimately informing clinical practice.

6. Conclusion

The study revealed a noteworthy association between the use of TCM and reduced risk of SARS-CoV-2 infection; it implies that TCM may serve as a prophylactic measure against COVID-19. In light of these findings, it is imperative to use contemporary scientific methods to identify the biologically active substances in these herbs that impede SARS-CoV-2 infection; their identification may help refine treatments that bolster immune responses and obstruct viral infection pathways. Such research may promote pharmaceutical development by elucidating and articulating the underlying action mechanisms through which these herbs affect COVID-19.

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Authors' contribution

YLC and BHC conceived and designed the study. YZ, SXZ, WS and HL contributed to the data collection, YT performed the statistical analyses. XXC and MR wrote the manuscript. DDZ revised the manuscript for important intellectual content. All the authors approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in the paper.

Appendix A. Supplementary material

Supplementary material to this article can be found online at......

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